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CURRENT STATUS OF LINKAGE FOR SCHIZOPHRENIA: POLYGENES OF VANISHINGLY SMALL EFFECT OR MULTIPLE FALSE POSITIVES ?

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A recent paper (Schizophrenia Linkage Collaborative Group for Chromosomes 3, 1996) adds to claims to have established linkage to various genetic markers for schizophrenia or schizo-affective disorder. As a collaborator I am impressed that the project has been possible and consider this reflects credit on the co-ordinator DF Levinson as well as each of the collaborating groups. However in contributing to the discussion and writing of the paper I found myself in a small minority in my interpretation of the findings, and in particular in dissent from the widely held assumption that a large number of genes contributing to susceptibility to psychosis are to be found, and that some linkages have already been established. My doubts arise in part from the nature of the evidence presented in the collaborative study, in part from inconsistencies already in the literature, and from general considerations concerning the epidemiological characteristics of the condition and the brain changes that have been associated with it.

CHROMOSOMES 3, 6 AND 8 COLLABORATIVE STUDY

Concerning the conclusions of the collaborative study my reservations are based not upon a detailed understanding of the statistical analysis (which in the case of "heterogeneity lod (Hlod) scores" has become a somewhat arcane pursuit) but on general scientific considerations concerning the nature of the hypothesis and the type of evidence that has been interpreted as positive. The hypothesis that for any one of the three regions there is a fraction (unspecified in magnitude) of families who will show linkage is a decidedly flexible one. The strengths/weaknesses of the the findings must surely be weighed against those that might have been obtained -

i) relative to previous positive reports the lod score could have increased. With a sample size of over 560 families the increase obviously could have been substantial. In fact for chromosome 6 the maximum Hlod for the combined sample (with an increase in sample size by a factor of 2.5) is now less (with narrow diagnostic criteria) than was originally reported (with broad criteria). For chromosome 8 the maximum lod score is less than that in the original sample although the sample size is greater by a factor of 14. By any criterion that takes into account magnitude of effect these are non-replications.

ii) the region of positive findings could have focused. There is no indication that this is the case. Table 4 indicates that a maximum two-point lod score occurs for each of the ten markers tested in at least one of the centres. Even to the eye of faith there is no consistent trend in table 4.

iii) the broad diagnostic model, on which Straub et al based their strongest conclusions, could have been supported, but is not.

The evidence for linkage is convincing only to those who come with expectations that are both positive and flexible. By any more precise expectation the findings are negative. The central point is that an increase in sample size by a factor of 2.5 for chromosome 6 and by a factor of 14 for chromosome 8 does not increase the significance of the findings. On this basis the findings constitute not support for linkage but evidence of statistical noise.

HOW MANY GENES FOR SCHIZOPHRENIA ARE THERE ?

The conclusions add to an already confusing picture in the literature. A number of positive claims for linkage and association have been advanced (eg for loci on 5q, 11q, PSAR, homozygosity at the D3 receptor, 6p, 22, mutations in the D2 receptor, 8p, 3p, AR, 13q and to the 5HT2A receptor) but for each such claim it is not difficult to identify a paper the negative findings of which are unexpected on the assumption that the original claim had some generality with respect to the condition as it occurs in the population (Table).

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TABLE

CLAIMS FOR LINKAGE AND ASSOCIATION IN SCHIZOPHRENIA

LOCUS/GENE	CLAIM	EXAMPLES OF DISCORDANT FINDINGS (usually the first and/or most salient discrepancy)
5q	Sherrington et al (1988)	St Clair et al (1989) McGuffin et al (1990)
11q	St Clair et al (1990)	Mulcrone et al (1996)
PSAR	Collinge et al (1991)	Wang et al (1993) Crow et al (1994)
D3 homozygosity	Crocq et al (1992)	Rietschel et al (1996)
6p	Straub et al (1995)	Riley et al (1996) Garner et al (1996)
22	Pulver et al (1994)	Polymeropoulos et al (1995) Kalsi et al (1995)
DRD2	Arinami et al (1994)	Asherson et al (1994) Gejman et al (1994)
8p	Pulver et al (1995)	Kunugi et al (1996)
3p	Pulver et al (1995)	Moises et al (1995) Kalsi et al (1996)
AR	Crow et al (1993)	Arranz et al (1995)
13q	Lin et al (1995)	
5HT2A	Williams et al (1996)	Nimgaonkar et al (1996)

The reason why these discrepancies have excited less concern regarding replicability than they might otherwise have done is of course because many authors are willing to accept that the condition is heterogeneous in nature and perhaps therefore in genetic origin, and that their own findings relate either to genes of "minor effect" or genes that are confined to their own local population or a sub-sample of it.

THE NATURE OF THE DISEASE

The following considerations caution against too ready acceptance of such arguments

1) From the WHO ten-country study of incidence Jablensky et al (1992) concluded: "...schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures and have clinical features that are more remarkable by their similarity across cultures than by their difference". It seems that in this respect schizophrenia differs from other common conditions such as coronary artery disease, diabetes and arthritis.

2) Three studies (Owens et al. 1985; Harvey et al. 1990; Daniel et al. 1991) agree in finding that enlargement of the cerebral ventricles applies to the patient group as a whole and not to a sub-group; there is no evidence of bimodality. Predisposition to schizophrenia in general is associated with changes in brain structure and perhaps brain shape.

3) Unlike Huntington's disease or Alzheimer-type dementia schizophrenia presents within the reproductive phase of life and is associated with a substantial biological disadvantage, greater in males than females (Vogel, 1979). Any predisposing gene therefore is exposed to a substantial selective pressure.

In each of these respects there is a degree of homogeneity about the condition that is difficult to reconcile with heterogeneity of genetic causation. If the disease is the outcome of a number of different genetic anomalies why do these each result in the same (possibly developmental) brain changes ? If in different populations the condition is the result of different constellations of genetic predisposition why is the incidence so similar ? Why are there no differential effects of environmental selection ?

I have argued (Crow, 1995b; Crow, 1995a) that these features all reflect a relationship between the genetics of psychosis and the speciation characteristic of language, and that language and psychosis have a common evolutionary origin (Crow, 1996) in the genetic mechanism that allowed the two hemispheres to develop with a degree of independence. The argument that a determinant of cerebral asymmetry is present in the restricted class of (non-pseudo-autosomal) X-Y homologous genes is strong (Crow, 1993; Corballis et al. 1996). The case that this is relevant to genetic predisposition to psychosis is weak in that linkage findings on the X chromosome (DeLisi et al. 1994; Crow et al. 1996) are no stronger than a number of the above claims relating to the autosomes. However in the absence of strong and replicated linkage findings the arguments for homogeneity of aetiology of psychosis and against too ready acceptance of multiple genetic origins deserve careful consideration.

CONCLUSION

There have been at least a dozen claims for linkage or association of schizophrenia/schizoaffective disorder to specific loci or genes; in each case there are contrary data which can be reconciled with the original report only on the basis that there are a large number of predisposing genes of small effect and/or that there is considerable heterogeneity between populations. But the brain changes associated with the disease are uniform and fail to identify a sub-population, and the incidence and most characteristic symptoms are constant across populations that have been separated for thousands of years. Moreover the genetic predisposition is under substantial (and sex-related) selective pressure.These considerations suggest a greater degree of homogeneity to the disease process than has been assumed in the recent genetic literature. The possibility that current claims for linkage or association are false positives and that a gene of major effect has yet to be discovered should be kept under review.

REFERENCES

Arinami T, Itokawa M, Enguchi H, Tagaya H, Sano S, Shimizu H, Hamaguchi H, Toru M (1994): Association of dopamine D2 receptor molecular variant with schizophrenia. Lancet 343:703-704.

Arranz M, Sharma T, Sham P, Kerwin R, Nanko S, Owen M, Collier D (1995): Schizophrenia and the androgen receptor gene: report of a sibship showing cosegregation with Reifenstein syndrome but no evidence for linkage in 23 multiply affected families. American Journal of Medical Genetics (Neuropsychiatric Genetics) 60:377-381.

Asherson P, Williams N, Roberts E, McGuffin P, Owen M (1994): DRD2 Ser311/Cys311 polymorphism in schizophrenia. Lancet 343:1045

Collinge J, DeLisi LE, Boccio A, Johnstone EC, Lane A, Larkin C, Leach M, Lofthouse R, Owen F, Poulter M, Shah T, Walsh C, Crow TJ (1991): Evidence for a pseudoautosomal locus for schizophrenia using the method of affected sibling pairs. British Journal of Psychiatry 158:624-629.

Corballis MC, Lee K, McManus IC, Crow TJ (1996): Location of the handedness gene on the X and Y chromosomes. American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:50-52.

Crocq MA, Mant R, Asherson P, Williams J, Hode Y, et al (1992): Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. Journal of Medical Genetics 29:858-60.

Crow TJ, Dann J, Laval SH, Loftus J, Devoto M, Vita A, Comazzi M, Morganti C, Boccio-Smith A, Shields G, De-Lisi LE (1996): Re-assessment of the X-Y model in 34 sibling pairs with schizophrenia or

schizo-affective disorder. Psychiatric Genetics 6:138(Abstract).

Crow TJ (1993): Sexual selection, Machiavellian intelligence and the origins of psychosis. Lancet 342:594-598.

Crow TJ, Poulter M, Lofthouse R, Chen G, Shah T, Bass N, Morganti C, Vita A, Smith C, Boccio-Smith A, Shields G, DeLisi LE (1993): Male siblings with schizophrenia share alleles at the androgen receptor above chance expectation. American Journal of Medical Genetics 48:159-160.

Crow TJ, DeLisi LE, Lofthouse R, Poulter M, Lehner T, Bass N, Shah T, Walsh C, Boccio-Smith A, Shields G, Ott J (1994): An examination of linkage of schizophrenia and schizoaffective disorder to the pseudo-autosomal region (Xp22.3). British Journal of Psychiatry 164:159-164.

Crow TJ (1995a): A continuum of psychosis, one human gene and not much else - the case for homogeneity. Schizophrenia Research 17:135-145.

Crow TJ (1995b): Constraints on concepts of pathogenesis: Language and the speciation process as the key to the etiology of schizophrenia. Archives of General Psychiatry 52:1011-1014.

Crow TJ (1996): Language and psychosis: common evolutionary origins. Endeavour 20(3):105-109.

Daniel DG, Goldberg TE, Gibbons RD, Weinberger DR (1991): Lack of a bimodal distribution of ventricular size in schizophrenia: A Gaussian mixture analysis of 1056 cases and controls. Biological Psychiatry 30:886-903.

DeLisi LE, Devoto M, Lofthouse R, Poulter M, Smith A, Shields, Bass N, Chen G, Vita A, Morganti C, Ott J, Crow TJ (1994): Search for linkage to schizophrenia on the X and Y chromosomes. American Journal of Medical Genetics (Neuropsychiatric Genetics) 54:113-121.

Garner C, Kelly M, Cardon L, Joslyn G, Carey A, LeDuc C, Lichter J, Harris T, Loftus J, Shields G, Comazzi M, Vita A, Smith AM, Dann J, Crow TJ, DeLisi LE (1996): Linkage analysis of schizophrenia to chromosome 6p24-p22: an attempt to replicate. American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:595-610.

Gejman PV, Ram A, Gelernter J, Friedman E, Cao Q, Pickar D, Blum K, Noble EP, Kranzler HR, O'Malley S, Hamer DH, Whitsitt F, Rao P, DeLisi LE, Virkkunen M, Linnoila M, Goldman D, Gershon ES (1994): No structural mutation in the D2 receptor gene in alcoholism or schizophrenia. JAMA 271:204-208.

Harvey I, McGuffin P, Williams M, Toone BK (1990): The ventricle-brain ratio (VBR) in functional psychoses: an admixture analysis. Psychiatry Research Neuroimaging 35:61-69.

Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A (1992): Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization Ten Country Study. Psychological Medicine Suppl 20:1-97.

Kalsi G, Brynjolffson J, Butler R, Sherrington R, Curtis D, Sigmundsson DT, Read T, Murphy P, Sharma T, Petursson H, Gurling HDM (1995): Linkage analysis of chromosome 22q12-13 in a United Kingdom/Iceland sample of 23 multiplex schizophrenia families. American Journal of Medical Genetics (Neuropsychiatric Genetics) 60:298-301.

Kalsi G, Curtis D, Brynjolfsson J, Sigmundsson T, Butler R, Read T, Murphy P, Petursson H, Gurling HMD (1996): Exclusion of linkage between schizophrenia and the putative chromosome 3p24-p26 susceptibility locus. Psychiatric Genetics 6:148(Abstract).

Kunugi H, Curtis D, Vallada HP, Nanko S, Powell JF, Murray RM, McGuffin P, Owen MJ, Gill M, Collier DA (1996): A linkage study of schizophrenia with DNA markers from chromosome 8p21-p22 in 25 multiplex families. Schizophrenia Research 22:61-68.

Lin MW, Curtis D, Williams N, Arranz M, Nanko S, Collier D, McGuffin P, Murray R, Owen M, Gill M, Powell J (1995): Suggestive evidence for linkage of schizophrenia to markers on chromosome 13q14.1-q32. Psychiatric Genetics 5:117-126.

McGuffin P, Sargeant M, Hetti S, Tidmarsh S, Whatley S, Marchbanks RM (1990): Exclusion of a schizophrenia susceptibility gene from the chromosome 5q11-q13 region: new data and a reanalysis of previous reports. American Journal of Human Genetics 47:524-535.

Moises HW, Yang L, Kristbjarnarson H, Wiese C, Byerley W, Macciardi F, Arolt V, Blackwood D, Lui X, Sjogren B, Aschauer HN, Hwu G, Yang K, Livesley WJ, Kennedy JL, Zoega T, Ivarsson O, Bui K, Yu M, Havsteen B, Commenges D, Weissenbach J,

Schwinger E, Gottesman II, Pakstis AJ, Wetterberg L, Kidd KK, Helgason T (1995): An international two-stage genome-wide search for schizophrenia susceptibility genes. Nature Genetics 11:321-324.

Nimgaonkar VL, Zhang XR, Brar JS, DeLeo M, Ganguli R (1996): 5-HT2 receptor gene locus: association with schizophrenia or treatment response not detected. Psychiatric Genetics 6:23-27.

Owens DGC, Johnstone EC, Crow TJ, Frith CD, Jagoe JR, Kreel L (1985): Cerebral ventricular enlargement in schizophrenia: relationship to the disease process and its clinical correlates. Psychological Medicine 15:27-41.

Polymeropoulos M, Coon H, DeLisi LE, Crow TJ, Gershon ES, Rubenstein J, Hoff M, Holis J, Boccio M, Shields G, Bass N, Poulter M, Lofthouse R, Byerley W, Merril C (1995): Search for a schizophrenia susceptibility locus on chromosome 22. American Journal of Medical Genetics (Neuropsychiatric Genetics) 54:93-99.

Pulver AE, Karayiorgou M, Wolyniec PS, Lasseter VK, Kasch L, Nestadt G, Antonorakis SE, Housman D, Kazazian HH, Meyers D, Ott J, et al (1994): Sequential strategy to identify a susceptibility gene for schizophrenia: report of a potential linkage on chromosome 22q12-q13.1: Part 1. American Journal of Medical Genetics (Neuropsychiatric Genetics) 54:36-43.

Pulver AE, Lasseter VK, Kasch L, Wolyniec P, Nestadt G, Blouin J, Kimberland M, Babb R, Vourlis S, Chen H, Lalioti M, Morris MA, Karayiorgou M, Ott J, Meyers D, Antonarakis SE, Housman D, Kazazian HH (1995): Schizophrenia: A genome scan targets chromosomes 3p and 8p as potential sites of susceptibility genes. American Journal of Medical Genetics (Neuropsychiatric Genetics) 60:252-260.

Rietschel M, Nothen MM, Albus M, Maier W, Minges J, Bondy B, Koerner J, Hemmer S, Fimmers R, Moeller HJ, Wildenauer D, Propping P (1996): Dopamine D-3 receptor Gly-9/Ser-9 polymorphism and schizophrenia: No increased frequency of homozygosity in German familial cases. Schizophrenia Research 20:181-186.

Riley BP, Rajagopalan S, Mogudi-Carter M, Jenkins T, Williamson R (1996): No evidence for linkage of chromosome 6p markers to schizophrenia in Southern African Bantu-speaking families. Psychiatric Genetics 6:41-49.

Schizophrenia Linkage Collaborative Group for Chromosomes 3 6a (1996): Additional support for schizophrenia linkage on chromosomes 6 and 8: A multicenter study. American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:580-594.

Sherrington R, Brynjolffson J, Petursson H, Potter M, Dudleston K, Barraclough B, Wasmuth J, et al (1988): Localization of a susceptibility locus for schizophrenia on chromosome 5. Nature 336:164-167.

St Clair D, Blackwood D, Muir W, Baillie D, Hubbard A, Wright A, Evans HJ (1989): No linkage of chromosome 5q11-q13 markers to schizophrenia in Scottish families. Nature 339:305-309.

St Clair D, Blackwood D, Muir W, Carothers A, Maura W, Spowart G, Gosden C, Evans HJ (1990): Association within a family of a balanced autosomal translocation with major mental illness. Lancet 336:13-16.

Straub RE, MacLean CJ, O'Neill FA, Burke J, Marphy B, Duke F, Shinkwin R, Webb BT, Zhang J, Walsh D, Kendler KS (1995): A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogenity. Nature Genetics 11:287-293.

Vogel HP (1979): Fertility and sibship size in a psychiatric patient population. Acta Psychiatrica Scandinavica 60:483-503.

Wang ZW, Black D, Andreasen NC, Crowe RR (1993): A linkage study of chromosome 11q in schizophrenia. Archives of General Psychiatry 50:212-216.

Williams J, Spurlock G, McGuffin P, Mallet J, Nothen MM, Gill M, Aschauer H, Nylander P, Macclardi F, Owen MJ (1996): Association between schizophrenia and T102C polymorphism of the 5-hydroxytryptamine type 2a-receptor gene. Lancet 347:1294

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